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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

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01/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/622,854	LI, CHIANG J.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,9-17,35,38,39,43-51,53 and 73-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-5,9-17,35,38-39,43-51,53 and 73-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-76 are presented for examination.

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed October 17, 2008 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-76 are pending. Claims 1, 35 and 53 are amended.

Applicant's arguments, filed October 17, 2008, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of a G1 or S phase checkpoint activator selected from 3,4-dihydro-4,4-dimethyl-2H-naphtho-[1,2-b]-thiopyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-2H-naphtho-[1,2-b]-thiopyran-5,6-dione; 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione; or beta-lapachone, for the treatment of prostate,

colon, breast, pancreatic or lung cancer in an amount effective to cause tumor regression, does not reasonably provide enablement for the administration of a G1 or S phase checkpoint activator to elevate the expression of an E2F transcription factor selected from the group consisting of E2F-1, E2F-2 or E2F-3 in cancerous cells but not affecting the viability of non-cancerous cells in said subject, for the reasons of record set forth at p.5-10 of the previous Office Action dated April 17, 2008, of which said reasons are herein incorporated by reference.

Newly amended claims 1 and 35 remain properly included in the present rejection because the claims are directed to the administration of a G1 or S phase checkpoint activator to a subject in need of treatment of prostate, colon, breast, pancreatic or lung cancer, wherein the activator is administered to elevate the expression of E2F-1 (claim 35) or a member of the E2F family of transcription factors, selected from E2F-1, E2F-2 or E2F-3 (claim 1), to activate a G1 or S phase checkpoint in cancerous cells but not in non-cancerous cells, wherein said elevation of a member of the E2F family of transcription factors and activation of a G1 or S phase checkpoint induced apoptosis in cancer cells but not in non-cancerous cells in the subject, and further wherein the checkpoint activator is not beta-lapachone. Accordingly, the claims are not only directed to the administration of the activator in such a manner (e.g., either by dose, route, etc.) to be capable of selectively activating a G1 or S phase checkpoint without inducing apoptosis in non-cancerous cells, but is also directed to the administration of the activator in such a way as to effect elevation of the expression of E2F transcription factors (i.e., E2F-1, E2F-2 or E2F-3).

Newly amended claim 53 remains properly included in the present rejection because the claims are directed to the administration of a G1 or S phase checkpoint activator to a subject in need of treatment of prostate, colon, breast, pancreatic or lung cancer, wherein the activator is administered to activate a G1 or S phase checkpoint and to induce apoptosis in cancer cells but wherein the checkpoint activator does not activate a G1 or S phase checkpoint and does not induce apoptosis in non-cancerous cells in the

subject, and further wherein the checkpoint activator is not beta-lapachone. Accordingly, the claims are directed to the administration of the activator in such a manner (e.g., either by dose, route, etc.) so as to be capable of selectively activating a G1 or S phase checkpoint, but without inducing apoptosis in non-cancerous cells.

The basis of the rejection set forth at p.9-11 of the previous Office Action dated March 22, 2007 and explained further at p. 5-10 of the previous Office Action dated April 17, 2008 remains proper despite Applicant's claim amendments because the claims now specifically require that the G1 or S phase checkpoint activator is administered to result in elevation of E2F transcription factor expression (specifically, E2F-1, E2F-2 or E2F-3), which activates a G1 or S phase checkpoint in cancerous cells (thereby causing apoptosis) but does not induce apoptosis in non-cancerous cells in the subject to be treated. However, it remains that Applicant has failed to provide any specific guidance or protocol in the accompanying specification that would be adequate direction to one of ordinary skill in the art at the time of the invention to determine how one would go about administering the claimed G1 or S phase checkpoint activator to achieve the claimed objective of treating cancer via elevating the expression of E2F-1, E2F-2 or E2F-3 to activate a G1 or S phase checkpoint in cancerous cells to cause apoptosis but not causing apoptosis in the non-cancerous cells of the subject treated.

There is a clear need for guidance in the instant specification as to how one of skill in the art would effectively administer the claimed G1 or S phase checkpoint activating therapy to treat cancer by elevating the expression of E2F transcription factors (i.e., E2F-1, E2F-2 or E2F-3) to cause apoptosis in cancerous cells but without causing apoptosis of non-cancerous cells in view of the state of the art at the time of the invention summarized at p.10-11 of the previous Office Action dated March 22, 2007, of which such reasons are herein incorporated by reference and will not be repeated herein in the interests of brevity.

Response to Applicant's Arguments

Applicant traverses the instant rejection, alleging that the specification readily describes that the G1 or S phase checkpoint activator is capable of selectively elevating an E2F transcription factor and selectively activating a G1 or S phase checkpoint to selectively induce apoptosis in a cancer cell without elevation of E2F or activation of a G1 or S phase checkpoint to induce apoptosis in non-cancerous cells. Applicant relies upon Ex.2 at p.34, l.9-p.36, l.6, Figs.7-11 and Table 1. Still further, Applicant relies upon the therapeutically effective dosage ranges at p.29, l.26-p.30, l.6 of the instant specification as guidance for this step of the claimed method and further alleges that the determination of specific amounts is well within the skill of the artisan.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Though the portions of the instant specification upon which Applicant presently relies for enabling direction have each been fully and carefully considered, it remains that, while such disclosure demonstrates a clear elevation in E2F transcription factor expression in cancerous cells (see, e.g., Example 2, p.34-36) versus non-cancerous cells, the exemplary embodiments presented at p.30-37 of the instant specification fail to provide any specific direction or guidance as to how one would effectively administer the claimed G1 or S phase checkpoint activator to achieve elevation of E2F expression and selectively induce apoptosis in cancerous cells only. Moreover, the "therapeutically effective dosage ranges" provided at p.29-30 of the instant specification are generically disclosed as being effective to "result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer" (p.29), but are silent as to whether such disclosed therapeutically effective dosage ranges are, in fact, additionally effective to elevate E2F expression while sparing non-cancerous cells from toxicity or reduced viability. In other words, what is clearly lacking from the instant disclosure, even in the exemplary embodiments upon which Applicant relies for enabling guidance, is

clear direction as to how one would be able to execute the method of the instant claims *without* causing apoptosis of non-cancerous cell(s) in the subject to be treated.

The fact remains that, given the discussion of the unpredictability in the art at the time of the instant invention, the art failed to recognize the ability to selectively induce apoptosis in cancerous cells in the absence of *apoptosis in non-cancerous or normal cells.* Please see, e.g., p.10 of the previous Office Action dated March 22, 2007, which stated that the art at the time of the invention acknowledged the complex nature of treating cancer in general and also the toxic nature of chemotherapeutic therapies, not only to the tumor itself, but also to the normal (i.e., non-cancerous) cells of the body, thus, resulting in numerous adverse side effects. As a result, one of ordinary skill in the art would have had reason to doubt Applicant's allegation that the checkpoint activator can be administered in such a manner to result in activation of a G1 or S phase checkpoint in cancer cells and thereby induce apoptosis or inhibit cellular proliferation without any effect whatsoever on non-cancerous cells, since each and every chemotherapeutic regimen available in the art is replete with toxic effects not only on the offending tumor, but also on the body as a whole. This is primarily due to the fact that the cytotoxic effects of the chemotherapeutic agents cannot be isolated or localized solely to the tumorigenic tissues and cells to be treated, absent specific and explicit direction or guidance by Applicant as to how such an objective could, in fact, be achieved.

Applicant fails to rebut this clear presumption of unpredictability and complexity in the art by providing any arguments and/or evidence, aside from Counsel's own speculation, that the instant examples and disclosed generic therapeutic dosages of the claimed G1 or S phase checkpoint activator would have been successful in elevating E2F expression in the absence of any toxicity or apoptosis of non-cancerous or normal cells. Though Applicant alleges in the instant remarks that the determination of a therapeutically effective amount capable of such a function would be well within the skill of the artisan, it remains that the art speaks to the contrary of this conclusion by supporting the general toxicity of

virtually all chemotherapeutic regimens (to cancerous and non-cancerous cells alike) such that the idea that Applicant's therapy would have no effect on non-cancerous cells would have been an outcome not reasonably expected by the skilled artisan. Accordingly, Applicant's opinion that the artisan would merely have needed to perform routine experimentation to determine such amounts is no more than an allegation without factual support and is further disputed in view of the fact that, absent any direction or guidance by Applicant as to how to go about determining such amounts with at least a reasonable expectation of success, the artisan would have needed to resort to random speculation to determine the scope of the amounts capable of the claimed function(s). As set forth in MPEP §2145, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

In view of the foregoing, when all of the evidence is considered, the totality of rebuttal evidence of enablement fails to outweigh the evidence in support of the instant conclusion of a lack of adequate enabling guidance presented in the instant specification.

For these reasons provided *supra*, and those previously made of record at p. 5-10 of the Office Action dated April 17, 2008, rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-76 remains proper and is **maintained**.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, 38-39, 43-51, 74 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claim 35 is directed to a method of treating prostate, colon, breast, pancreatic or lung cancer comprising the administration of a G1 or S phase checkpoint activator to a subject in need thereof, wherein said checkpoint activator is administered to elevate the expression of an E2F-1 transcription factor, to activate a G1 or S phase checkpoint in cancerous cells but not in non-cancerous cells, wherein said elevation of a member of the E2F family of transcription factors and activation of a G1 or S phase checkpoint induces apoptosis in cancer cells but not in non-cancerous cells in said subject, and further wherein said checkpoint activator is not beta-lapachone.

In particular, it is noted that instant claim 35 recites that the G1 or S phase checkpoint activator is administered with the purpose of elevating the expression of an E2F-1 transcription factor, but then goes on to state that the elevation of a member of the E2F family of transcription factors induces apoptosis in cancer cells but not in non-cancerous cells. It is unclear whether the activator is administered to elevate the expression of, specifically, the E2F-1 transcription factor or whether it is administered to elevate the expression of any member of the E2F family of transcription factors (e.g., such as E2F-1, E2F-2, E2F-3, etc.). Accordingly, the transcription factor(s) that is intended to be elevated by the G1 or S phase checkpoint activator is not clearly, precisely or deliberately set forth within the text of the claim and, thus, one of ordinary skill in the art at the time of the invention would not have been reasonably apprised of the metes and bounds of the subject matter for which Applicant is presently seeking protection.

Furthermore, the term "the E2F family of transcription factors" lacks sufficient antecedent basis, since the preceding text of the claim only sets forth a reference to "an E2F-1 transcription factor", not an "E2F family of transcription factors" *per se*.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remain rejected under 35 U.S.C. 102(a) as being anticipated by Jiang et al. (WO 03/011224; February 2003) in light of Jacob ("Paclitaxel", Pharmacology, 4th Ed., 1996; p.268), cited to show a fact, each already of record, for the reasons of record set forth at p.10-14 of the previous Office Action dated April 17, 2008, of which said reasons are herein incorporated by reference.

Newly amended claims 1, 35 and 53 remain properly rejected because Applicant has amended part (c) of each of claims 1 and 35 and part (b) of claim 53 to now read upon the checkpoint activator being administered (1) to elevate the expression of an E2F transcription factor for activating a G1 or S phase checkpoint to induce apoptosis in cancerous cells but not in non-cancerous cells (claims 1 or 35) or (2) to activate a G1 or S phase checkpoint to induce apoptosis in cancer cells but not induce apoptosis in non-cancerous cells (claim 53). In each of claims 1, 35 or 53, such statements circumscribe a function of the G1 or S phase checkpoint activator when administered in the manner specifically recited in the instant claims. In other words, the administration of the claimed G1 or S phase checkpoint activator according to the claimed invention results in the claimed function(S) of the activator to elevate E2F expression to activate a G1 or S phase checkpoint to induce apoptosis in cancer cells, while sparing non-cancerous cells from apoptosis.

In view of these reasons, whatever properties or characteristics of the claimed compound [i.e., 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione] that Applicant has attributed to such a compound, i.e., that

it functions to elevate E2F expression to activate a G1 or S phase checkpoint to induce apoptosis, are necessarily present in the method of using this same compound in a therapeutic amount for the same therapeutic purpose as disclosed by Jiang et al., absent factual evidence to the contrary, because properties or effects of a compound are not severable from the compound itself, particularly when it is administered under identical conditions (i.e., same host, same amount, etc.). Please see MPEP §2112.

The explanation of the effect obtained when using a compound (i.e., that it activates a G1 or S phase checkpoint, elevates expression of E2F transcription factors, inducing apoptosis in cancer cells, but does not induce apoptosis in non-cancerous cells) cannot confer novelty on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the selective checkpoint activation, E2F transcription factor elevation, apoptosis-induction and lack of apoptotic effect on non-cancerous cells was not itself recognized as a pharmacological effect of administering the disclosed compound of Jiang et al. for any one of the therapeutic purposes discussed therein, such an effect is not considered a new therapeutic application because a known therapeutic effect and benefit of using this same active agent in the same host in a therapeutic amount for treating the same disorder was already known in the prior art. Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or a combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the face that such a mechanistic property may not have been readily apparent to, or recognized by, one of ordinary skill in the art at the time of the disclosure.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Jiang et al. fails to teach, explicitly or inherently, the administration of a G1 or S phase checkpoint activator that selectively elevates an E2F transcription factor (selected from E2F-1, E2F-2 or E2F-3), selectively activates a G1 or S phase checkpoint and selectively induces apoptosis in cancerous cells without elevating E2F, activating a G1 or S phase checkpoint or inducing apoptosis in non-cancerous cells, as required by the instant claims.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Initially, it is noted that, though the apoptosis-inducing effect and E2F expression-elevating effect of the 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone (also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione as recited in the instant claims) without affecting non-cancerous cells are not explicitly noted in the cited reference, it is noted that the very teaching of the identical manner of administration of the identical compound(s) to those presently claimed in the same host in a therapeutic amount for treating the same condition as claimed in said host must necessarily possess such apoptosis-inducing and E2F expression elevating effects without affecting such non-cancerous cells, even though such properties may not have been appreciated by the patentee at the time of the invention. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host in the same total amount. Please reference MPEP §2112.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure

at the time of invention, so long as the subject matter stated to be present in the normal and usual course of execution of the disclosed method is, indeed, present. In other words, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated and/or rendered obvious by the prior art method. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). The Examiner herein incorporates by reference the explanation provided *supra* as to why the claimed effects of inducing apoptosis, activation of the claimed checkpoints and elevating E2F transcription expression would have been necessarily performed in the prior art method to Jiang et al. In the interests of brevity, such reasons will not be herein repeated so as not to burden the record.

Moreover, Applicant fails to advance any specific reasons or evidence, aside from Counsel's own allegation, in support of this position that the presently claimed properties of inducing apoptosis and elevating E2F expression without affecting non-cancerous cells are not necessarily present in the disclosure of Jiang et al. This assertion by Counsel is an unsupported allegation and fails to take the place of evidence in the record. Statements of this nature are clearly unpersuasive in accordance with the guidance provided at MPEP §2145, which states, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)". Accordingly, there is no reason or basis advanced by Applicant to reasonably doubt, in view of the reasons clearly set forth *supra*, that such properties are not, in fact, necessarily present in the invention disclosed by Jiang et al. and, as a result, such an argument is unpersuasive in establishing novelty of the claimed invention.

Furthermore, for the record, Applicant is reminded that, whatever the merit of the scientific

teaching provided by the application regarding the mechanism of action of the claimed compound, it is only the therapeutic effect of the medicament (i.e., treating the instantly claimed cancers), which is material to the assessment of novelty within the meaning of 35 U.S.C. 102. The use of a compound for the treatment of a specified disease can only be validly claimed as an invention once and cannot be validly claimed subsequently again for the treatment of the same disease under the guise of another or newly specified pharmacological mechanism. In fact, the discovery of a new way of action of a compound amounts only to an explanation of the technical biologic effect, since the ultimate therapeutic effect obtained from its use remains the same. Importantly, since the therapeutic effect here is clearly identical for the reasons explained *supra*, the use of the compound in this manner is *not changed* by the discovery or identification of the mechanism by which it operates.

For the reasons provided *supra*, and those previously made of record at p.10-14 of the Office Action dated April 17, 2008, rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-74 remains proper and is **maintained**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 15-17, 35 and 49-51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Jiang et al. (WO 03/011224; February 2003) in view of Pardee et al. (WO 00/61142; 2000), each already of record, for the reasons of record set forth at p.14-18 of the previous Office Action dated April 17, 2008, of which said reasons are herein incorporated by reference.

Newly amended claims 1, 35 and 53 remain properly rejected because Applicant has amended part (c) of each of claims 1 and 35 and part (b) of claim 53 to now read upon the checkpoint activator being administered (1) to elevate the expression of an E2F transcription factor for activating a G1 or S phase checkpoint to induce apoptosis in cancerous cells but not in non-cancerous cells (claims 1 or 35) or (2) to activate a G1 or S phase checkpoint to induce apoptosis in cancer cells but does not induce apoptosis in non-cancerous cells (claim 53). In each of claims 1, 35 or 53, such statements circumscribe a function of the G1 or S phase checkpoint activator when administered in the manner specifically recited in the instant claims. In other words, the administration of the claimed G1 or S phase checkpoint activator according to the claimed invention results in the claimed function(s) of the activator to elevate E2F expression to activate a G1 or S phase checkpoint to induce apoptosis in cancer cells, while sparing non-cancerous cells from apoptosis.

In view of these reasons, whatever properties or characteristics of the claimed compound [i.e., 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone, also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione] that Applicant has attributed to such a compound, i.e., that it functions to elevate E2F expression to activate a G1 or S phase checkpoint to induce apoptosis, are necessarily present in the method of using this same compound in a therapeutic amount for the same therapeutic purpose as disclosed by Jiang et al., absent factual evidence to the contrary, because properties or effects of a compound are not severable from the compound itself, particularly when it is administered under identical conditions (i.e., same host, same amount, etc.). Please see MPEP §2112.

The explanation of the effect obtained when using a compound (i.e., that it activates a G1 or S phase checkpoint, elevates expression of E2F transcription factors, induces apoptosis in cancer cells and does not affect non-cancerous cells) cannot confer non-obviousness on a known process if the skilled artisan was already aware of the occurrence of the desired therapeutic effect. In other words, even if the checkpoint activation, E2F transcription factor elevation, apoptosis induction and lack of effect on non-

cancerous cells was not itself recognized as a pharmacological effect of administering the disclosed compound of Jiang et al. for any one of the therapeutic purposes discussed therein, such an effect is not considered a new therapeutic application because a known therapeutic effect and benefit of using this same active agent in the same host in a therapeutic amount for treating the same disorder of said host was already known in the prior art. Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 103 is based upon the therapeutic applications and effects of the compounds, not the mechanism by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, or a combination of chemical compounds, when administered under identical conditions, is necessarily present, despite the face that such a mechanistic property may not have been readily apparent to, or recognized by, one of ordinary skill in the art at the time of the disclosure.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Jiang et al. fails to teach, explicitly or inherently, the administration of a G1 or S phase checkpoint activator that selectively elevates an E2F transcription factor (selected from E2F-1, E2F-2 or E2F-3), selectively activates a G1 or S phase checkpoint and selectively induces apoptosis in cancerous cells without elevating E2F, activating a G1 or S phase checkpoint or inducing apoptosis in non-cancerous cells, as required by the instant claims. Applicant further submits that Pardee fails to cure these deficiencies.

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Initially, it is noted that, though the apoptosis-inducing effect and E2F expression-elevating effect of the 3-(3-methyl-2-butenyl)-4-methyl-beta-lapachone (also known as 3,4-dihydro-2,2-dimethyl-3-(3-methyl-2-butenyl)-2H-naphtho-[1,2-b]-pyran-5,6-dione as recited in the instant claims) without affecting

non-cancerous cells are not explicitly noted in the cited reference, it is noted that the very teaching of the identical manner of administration of the identical compound(s) to those presently claimed in the same host in a therapeutic amount for treating the same condition as claimed in said host must necessarily possess such apoptosis-inducing and E2F expression elevating effects without affecting such non-cancerous cells, even though such properties may not have been appreciated by the patentee at the time of the invention. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstances or, in the present case, the same host in the same total amount. Please reference MPEP §2112.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, so long as the subject matter stated to be present in the normal and usual course of execution of the disclosed method is, indeed, present. In other words, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated and/or rendered obvious by the prior art method. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). The Examiner herein incorporates by reference the explanation provided *supra* as to why the claimed effects of inducing apoptosis, activation of the claimed checkpoints and elevating E2F

transcription expression would have been necessarily performed in the prior art method to Jiang et al. In the interests of brevity, such reasons will not be herein repeated so as not to burden the record.

Moreover, Applicant fails to advance any specific reasons or evidence, aside from Counsel's own allegation, in support of this position that the presently claimed properties of inducing apoptosis and elevating E2F expression without affecting non-cancerous cells are not necessarily present in the disclosure of Jiang et al. This assertion by Counsel is an unsupported allegation and fails to take the place of evidence in the record. Statements of this nature are clearly unpersuasive in accordance with the guidance provided at MPEP §2145, which states, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)". Accordingly, there is no reason or basis advanced by Applicant to reasonably doubt, in view of the reasons clearly set forth *supra*, that such properties are not, in fact, necessarily present in the invention disclosed by Jiang et al. and, as a result, such an argument is unpersuasive in establishing novelty of the claimed invention.

Furthermore, for the record, Applicant is reminded that, whatever the merit of the scientific teaching provided by the application regarding the mechanism of action of the claimed compound, it is only the therapeutic effect of the medicament (i.e., treating the instantly claimed cancers), which is material to the assessment of nonobviousness within the meaning of 35 U.S.C. 103. The use of a compound for the treatment of a specified disease can only be validly claimed as an invention once and cannot be validly claimed subsequently again for the treatment of the same disease under the guise of another or newly specified pharmacological mechanism. In fact, the discovery of a new way of action of a compound amounts only to an explanation of the technical biologic effect, since the ultimate therapeutic effect obtained from its use remains the same. Importantly, since the therapeutic effect here is clearly identical for the reasons explained *supra*, the use of the compound in this manner is *not changed* by the discovery or identification of the mechanism by which it operates.

Lastly, in response to Applicant's arguments that the reference to Pardee et al. fails to disclose the use of a G1 or S phase checkpoint activator to elevate the expression of a member of the E2F family of transcription factors to induce apoptosis in cancer cells but not in non-cancerous cells, such remarks are directed toward the individual teachings of the reference without considering the reference as it was combined with the primary reference to Jiang et al. Applicant is again reminded that rejections made under 35 U.S.C. 103(a) are based upon the combination of references. As a result, focusing solely on the discrete teachings of each of the cited references is tantamount to examining each of them inside of a vacuum and fails to be persuasive in establishing non-obviousness because it is the *combined* teachings that are the basis for a proper conclusion of obviousness, not each individual reference alone. In other words, it must be remembered that the references are relied upon in combination and are not meant to be considered separately. To properly conclude obviousness of an invention *does not require the claimed invention to be expressly suggested in its entirety by any one single reference under 35 U.S.C. 103(a)*. Rather, the test is *what the combined teachings* of the references would have suggested to those of ordinary skill in the art. Please reference *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968) and *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For these reasons, and those previously made of record at p.14-18 of the Office Action dated April 17, 2008, rejection of claims 1, 15-17, 35 and 49-51 remains proper and is **maintained**.

Conclusion

Rejection of claims 1, 4-5, 9-17, 35, 38-39, 43-51, 53 and 73-76 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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January 13, 2009

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